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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/725,214
Filing Date: December 01, 2003
Appellants: NAIR ET AL.

Ian C. McLeod
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 5, 2007 appealing from the Office action mailed January 10, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The amendment after final rejection filed on April 23, 2007 has been entered

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Listing of evidence relied upon:

Gorman, C. "How to Tell the Hype from the Hope: A Special Report", Time (1998), pp 37-45.

Gura, T. "Cancer Models: Systems for Identifying New Drugs are Often Faulty", Science (1997), vol. 279, pp. 1041-1042.

Jain, R. K. "Delivery of Molecular Models to Solid Tumors", Science (1996), vol. 271, pp. 1079-1080.

Katsube, N. et al. "Induction of Apoptosis in Cancer Cells by Bilberry (*Vaccinium myrtilus* and the Anthocyanins", Journal of Agricultural and Food Science (Jan 1, 2003), vol. 51, no. 1, pp. 68-75.

Oshima, M. et al., "Suppression of Intestinal Polyposis in $Apc^{\Delta 716}$ Knockout Mice by Inhibition of Cyclooxygenase 2 (COX-2)", Cell (1996), vol. 87, pp. 803-809.

Korobi, M. et al., "*In Vitro*-Screening for Cancer-Suppressive Effect of Food Components", JARQ (2003), vol. 37, no. 3, pp. 159-165.

Hou, D. –X. et al., "Anthocyanidins Inhibit Cyclooxgenase-2 Expression in LPS-evoked Macrophage : Structure-Activity Relationship and Molecular Mechanisms Involved", Biochemical Pharmacology (2005), vol. 70, pp. 417-425.

(9) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

Claims 1 and 5-7 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inhibiting the proliferation of HCT-116 colon cancer cells and AGS stomach cancer cells comprising contacting the cells with an effective amount of a composition consisting essentially of malvidin, does not reasonably provide enablement for a method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of any and all colon cells and/or any and all stomach cancer cells which comprises providing an effective amount of malvidin as an active ingredient to the mammal so as to inhibit the proliferation of the cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Nature of the Invention. The claims are drawn to a method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells which comprises: providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal so as to suppress the multiplicity of the cells. The claims are further drawn to wherein the cells are in a mammal and the malvidin is fed orally to the mammal; and, wherein the composition is in a pharmaceutical carrier; and wherein the stomach cell is AGS and the colon cell is HCT 116 both as maintained by the American Type Culture Collection.

Breadth of the Claims. The claims are broad in that the multiplicity of any and all stomach or colon cancer cells in both the stomach and colon of a mammal is suppressed comprising the administration of an effective amount of a composition which consists essentially of malvidin as an active ingredient is administered to a mammal so as to provide a method for *in vivo* suppression in a mammal of multiplicity of the aforementioned cancerous cells. The complex nature of the subject matter of the invention is clearly exacerbated by the breadth of the claims.

Guidance of the Specification and Existence of Working Examples. The specification envisions that the oral administration of a therapeutically effective amount of a composition to a mammal bearing cancerous cells in the stomach or colon, or both in the stomach and the colon will provide a method for the *in vivo* suppression in a mammal multiplicity in the stomach or the colon, or both in the stomach in the colon of cancer cells comprising the administration of an effective amount of a composition

consisting essentially of malvidin as an active ingredient to the mammal so as to suppress multiplicity of the cancerous cells.

While, Appellants have reasonably disclosed an *in vitro* method for inhibiting the proliferation of colon cancer (HCT-116) cells and stomach (AGS) cancer cells comprising incubating the American Type Culture Collection (Rockville, MD) human cancer cell lines in the presence of malvidin, Appellants have not demonstrated an *in vivo* method comprising orally administering an effective amount of a composition consisting essentially of malvidin to a mammal to provide the claimed beneficial functional effect for the suppression in a mammal of multiplicity in either the stomach or the colon, much less suppression in both the stomach and the colon of either HCT-116 colon cancer cells or AGS stomach colon cancer cells, much less suppression of multiplicity in either the stomach or the colon of any and all colon cancer cells or stomach cancer cells. For example, at [0043] of the present application, Appellants disclose, "Malvidin and pelargonidin were in particular found to be excellent inhibitors of stomach and colon cancer cell lines *in vitro*." However, nowhere in the present specification, as originally filed, do Appellants disclose a method comprising the oral administration of an effective amount of a composition consisting essentially of malvidin to a mammal in need thereof to suppress in a mammal multiplicity in either stomach or colon cancer cells therein the mammal or data there from. Instead, Appellants disclose only an *in vitro* method for the inhibition of the proliferation of colon (HCT) and stomach (AGS) cancer cells comprising contacting the human cancer cell lines in the presence of dose amounts of malvidin. Given the limited data as to the cancer model used to

assess the efficacy of the disclosed composition and the limited disclosure other than the mere mention that the disclosed compositions were inhibitors of the claim-designated human stomach and colon cancer cell lines *in vitro*, it seems highly unlikely that one of skill in the art would be able to use the claim-designated composition for the *in vivo* suppression in a mammal multiplicity in either the stomach and/or colon of the claim-designated human stomach and/or colon cancer cell lines, much less any and all stomach and/or colon cancer cells, comprising providing the mammal with an effective amount of a composition consisting essentially of malvidin, even after extensive experimentation.

Predictability and State of the Art. It should be noted that the state of the art at the time of filing of the present specification suggested that the delivery of therapeutic drugs which exhibit anti-tumor activity in cancer models do not necessarily have the same beneficial functional effect in humans as disclosed by Fredic Golden (Gorman, Christine. Cancer, "How to tell the hype from the hope: A Special Report", Time, 1998, pages 37-46.) and as disclosed by Trisha Gura ("Cancer Models: Systems for Identifying New Drugs are Often Faulty", Science, 1997, Vol. 278, pages 1041-1042.). Gura further discloses various different cancer models other than murine cancer models that are not predictive of the anti-cancer activity of potential anticancer agents when delivered to humans. In another instance, Jain (Jain, Rakesh K., "Delivery of molecular medicine to solid tumors", Science (1996), Vol. 271, pages 1079-1080.) discloses that while promising chemotherapeutic agents exhibit activity against cancer cells *in vitro* and *in vivo* tumor systems, these same agents heralded as breakthrough drugs do not

have the same functional effect in humans when delivered to humans bearing tumors. Moreover, while Appellant discloses malvidin as an inhibitor of colon cells, Katsube et al. (Katsube, N. et al. Journal of Agricultural and Food Chemistry (1/1/2003), 51(1): 68-75. Induction of apoptosis in cancer cells by bilberry (Vaccinium myrtillus) and the anthocyanins.) teaches, "Only pure delphindin and the glycoside isolated from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of HCT 116 cells".

Amount of Experimentation Necessary. The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or instant specification to teach how to make and/or use the instantly claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and both the stomach and the colon of cancer cells which comprises providing an effective amount of a composition which consists essentially of malvidin as an active ingredient to the mammal so as to suppress multiplicity of the cells. There is no guidance in the specification, other than the aforementioned examples directed to an *in vitro* method for inhibiting the proliferation of human cell lines of stomach and colon cancer comprising contacting the cells with a dose amount of a composition consisting essentially of malvidin. Given the insufficient guidance in the specification as to how to carry out the instantly claimed invention, the lack of working examples, the lack of correlative working examples, and the state of the art at the time the specification was filed, the claimed method for the *in vivo* suppression of multiplicity of either or both of any and all stomach and any and all colon cancer cells in a mammal comprising the

administration of an effective amount of the claim-designated composition would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

Accordingly, it would take undue experimentation without a reasonable expectation of success for one of skill in the art to provide the claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of any and all stomach and/or any and all stomach cancer cells or the claim-designated AGS stomach cancer cell line or the claim-designated HCT 116 colon cancer cell line comprising providing the mammal with an effective amount of a composition consisting essentially of malvidin to suppress multiplicity of the cancerous cells, as broadly claimed by Appellants.

(10) Response to Argument

With respect to the rejection of Claims 1 and 5-7 made under 35 U.S.C. § 112, first paragraph, Appellants' main argument is directed to the idea that the initial burden on the Examiner to give reasons that the specification lacks enablement for the instantly claimed method of treatment was not properly addressed in the Office action mailed on January 10, 2007. Thus, Appellants argue that Appellants have provided a showing that the claimed subject matter was described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; and, thereby Appellants request reversal of the Final Rejection set forth in the previous Office action. In an attempt to reverse the

present rejection and in attempt to establish that the instant disclosure satisfies the enablement requirement and enables any person skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention commensurate in scope with the claims without any necessary undue experimentation, Appellants consider each of the factors as applied by the Examiner under the *Wands* analysis.

All of Appellant's arguments, as well as the Declarations under 37 C.F.R. §1.132 filed on October 6, 2006 and on June 29, 2006 with their accompanying exhibits, have been thoroughly considered. However, the rejection remains the same for the reason set forth in the previous Office action and for all of the reasons set forth herein. Please note that the reasons have been slightly altered to take into consideration all of the above-mentioned arguments respectfully presented by Appellants in the Reply Brief.

Appellants' arguments that the Examiner has not come forward with any particular reasons or evidence to demonstrate that the claimed *in vivo* method for suppressing adenoma multiplicity of either or both of cancer cells in the stomach and colon of a mammal comprising providing an effective amount of a composition consisting essentially of malvidin so as to suppress the multiplicity of the cells are found unwarranted. The Examiner clearly established that the specification as originally filed did not satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, because all of the most relevant Wands factors were properly addressed and properly analyzed to support a conclusion of nonenablement of the invention, as broadly claimed by Appellants in the Final Rejection.

Breadth of the Claims. In addressing "the "*Breadth of the Claims*, at page 7, line 12 to page 16 of the Appeal Brief, Appellants state, "The claim breadth is limited to multiplicity in the stomach and/or colon. The composition provided to the mammal is narrowly limited to a composition which consists essentially of malvidin."

The examiner agrees with Appellants' statement of the breadth of the claims.

Nature of the Invention. With regard to the "Nature of the Invention", Appellants argue case law and cite the M.P.E.P (M.P.E.P. §2164.05(a) and M.P.E.P. §2164.05(b)). In considering the teachings of the abstract of Barranco et al. (*Invest. New Drugs*, 1983, vol. 1, pp 117-127) and the teachings of the abstract of Barranco et al. (*Cancer Res.*, 1983, vol. 43, pp. 1703-1709), Appellants further argue that the level of one of ordinary skill relating to the suppression of a multiplicity of cancer cells in the stomach and/or colon was high at the time the application was filed. Given the teachings of each of the reference of Barranco et al., Appellants conclude that it is clear that there is a high level of skill in this field, since both references teach that specific cellular models have been established that relate to specific cancers, namely gastric carcinoma in humans.

In response to Appellant's argument that the level of one of ordinary skill in the art relating the suppression of a multiplicity of cancer cells in the stomach and/or colon was high at the time the application was originally filed, again the Examiner looks to the aforementioned cited abstracts of Barranco et al. to look for such a teaching. Appellants' argument has been fully considered but found unpersuasive for the following

reasons. In consideration of the teachings of the abstract of Barranco et al. (*Invest. New Drugs*, 1983, vol. 1, pp 117-127), the limited disclosure merely concludes, "The studies reported here indicate that this human stomach cancer model can provide valuable insight [emphasis] into the design of clinical protocols for treatment of gastric carcinoma in man." Similarly, the abstract of Barranco et al. (*Cancer Res.*, 1983, vol. 43, pp. 1703-1709) merely concludes, "The identification of the mechanisms of drug sensitivity and resistance and the testing of drug and radiation combination treatment schedules into the design of clinical protocols for treatment of stomach cancer in humans." Nowhere in the limited disclosure of either of the cited references is there any indication that either one of ordinary skill in the art or the skilled artisan practicing the suppression of a multiplicity of cancer cells in the stomach and/or colon would be able to use the reference *in vitro* cancer cell line models to extrapolate the claimed *in vitro* model of cancer suppression of such cancer cells in a mammal comprising the oral administration of an effective amount of a composition consisting essentially of malvidin to the mammal, especially given that Barranco et al. (*Invest. New Drugs*, 1983, vol. 1, pp 117-127) teach that the clones of the human stomach cancer cell lines expressed heterogeneous survival responses to each of six tested anticancer agents, despite the fact that the cell lines had similar growth properties, morphologies and modal chromosome numbers.

Guidance of the Specification and Existence of Working Examples. With regard to "Guidance of the Specification and Existence of Working Examples", at page 9

of the Appeal Brief, line 4 to line 17, Appellants cite the M.P.E.P (M.P.E.P. §2164.03) and argue case law (*In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). For instance, Appellants argue:

"According to MPEP 2164.03, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required."

Appellants direct the Office to a Supplemental Declaration under 37 C.F.R. §1.132, filed October 6, 2006 to establish that the present disclosure provides sufficient guidance or direction to enable the skilled artisan to make and use the instantly claimed method of treatment based on the amount of knowledge in the art and the predictability in the art state of the art at the time of filing of the present application. Based on the teachings of Kang et al. (*Cancer Letters*, 2003, vol. 194, pp. 13-19), Appellants argue that Kang shows that there is a direct correlation between *in vitro* and oral *in vivo* use in suppressing multiplicity of human cancer cells of the stomach or colon with anthocyanins and cyanidin. Appellants further direct the Office to the first paragraph of the Supplemental Declaration, and Figures 1 and 2 of the specification, wherein malvidin is disclosed as a compound related to cyanidin. Appellants conclude "that there is predictability in the art of *in vivo* suppression of multiplicity of cancer cells in the stomach and/or colon, where *in vitro* tests have been performed and show that the activity of the a cancer treatment against stomach (AGS) or colon (HCT-116) cancer cell line".

Next Appellants direct the Office to paragraph [0043] of the specification on page 15 and Figure 7, stating that both malvidin and pelargonidin were found to be excellent inhibitors of stomach and colon cancer lines *in vitro*. Appellants further indicate that Figure 7 illustrates that the percentage of cell viability of the stomach (AGS) and colon (HCT-116) cancer cell lines dropped below 40% when 200 ppm malvidin was used. Appellants also refers to an enclosed Declaration under 37 C.F.R. §1.132, filed June 29, 2006, "that shows that the cell lines of HCT-116 and AGS are recognized as correlating to the specific conditions of human colon cancer and human stomach cancer, respectively".

Appellants also point the Office to paragraphs 4 and 6 of the declaration filed on June 29, 2006, referring to the ATCC (American Type Culture Collection, Rockville MD) Product Descriptions of Exhibit A, which describe a colon cell line designated HCT-116 and a stomach cell line designated AGS. Appellants argue that the teachings of Gieseg et al. (*BMC Cancer, 2004*, vol. 15, no. 4, pp.35. "*The Influence of Tumor Size and Environment on Gene Expression in Commonly Used Human Tumor Lines*".) provide evidence that HCT-116 is an *in-vitro* model that is recognized as correlating to the specific condition of colon cancer. Appellants also argue that each of the teachings of Barranco et al. (*Invest. New Drugs*, 1983, vol. 1, pp 117-127. "*Heterogeneous responses of an model of human stomach cancer to anticancer drugs*"; and, *Cancer Res.*, 1983, vol. 43, pp. 1703-1709. "*Establishment and Characterization of an In Vitro Model System for Human Adenocarcinoma of the Stomach*".) provides evidence that

AGS is an *in-vitro* model that is recognized in the art as correlating to the specific condition of stomach cancer.

On page 12, line 9 of the Appeal Brief to page 14, line 12, with particular regard to "*Existence of Working Examples*", Appellants cite the guidance of the M.P.E.P. and argues case law:

"According to MPEP § 2164.02, the issue of "correlation" is related to the issue of the presence or absence of working examples. 'Correlation" refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka,* 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Given that the particular cell lines taught in the Examples are recognized as models correlating to the specific conditions of the claimed methods, it is believed that the specification provides enablement for the claimed methods for *in vivo* inhibition in a mammal.

M.P.E.P. § 2164.02 also states that the lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. An applicant need not have actually reduced the invention to practice prior to filing. Compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski,* 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). "

In response to Appellants' argument that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art, the M.P.E.P. states: "It is common that doubt arises about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why the missing information is needed to provide enablement" [See M.P.E.P. 2164.06(a)].

With respect to Appellants' argument that the teachings of Kang et al. (*Cancer Letters*, 2003; vol. 194, pp. 13-19. Kang, Soo-Young et al. *Tart cherry anthocyanins inhibit tumor development in Apc^{Min} mice and reduce proliferation of human colon cancer cells.*) establish that there is predictability in the art of *in vivo* suppression of multiplicity of cancer cells of the stomach and/or colon where *in vitro* tests have been performed that show the activity of a cancer treatment against stomach (AGS) or colon (HCT-116) cancer cell lines because 'cyanidin' is a compound related to malvidin, the Examiner notes that Figures 1 and 2 of the specification show differences between the structural makeup of cyanidin and malvidin in relationship to their corresponding R_1 and R_2 groups. Such differences in the molecular structures of cyanidin and malvidin would not *necessarily* lead one skilled in the art, in the absence of a showing clearly demonstrating that the structural disparity between the two compounds exhibit the same functional effect for suppression of multiplicity of either stomach and/or colon cancer cells in both *in vitro* and *in vivo* test models, to reasonably predict that the oral

administration of an effective of malvidin to a mammal would provide the same beneficial effect exhibited by cyanidin tested *in vitro* and *in vivo* models. For instance, the R_1 group and the R_2 group of cyanidin correspond to H_1 and OH, respectively, whereas the R_1 group and the R_2 group of malvidin both correspond to OCH_3. Given the differences in the molecular structure of cyanidin and malvidin, the skilled artisan could not reasonably predict what these differences in molecular structures would have on the function of malvidin to provide the same or similar therapeutic effect exhibited by cyanidin to suppress the multiplicity of either colon cells or stomach cells or both colon and stomach cells in a mammal comprising the administration of an effective amount of a composition consisting essential of malvidin. Moreover, while Appellant vigorously argues that the scope of the required enablement required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required, Appellants are silent as to the Examiner's presentation of the reference of Katsube et al. set before them. Although Appellants disclose malvidin as an inhibitor of the multiplicity of colon cells, Katsube et al., teaches, "Only pure delphinidin and the glycoside isolated from the bilberry extract, but not the malvidin and the glycoside, inhibited the growth of HCT 116 cells." *See* abstract and Figure 6. Appellants' silence does not explain away what is disclosed in the present disclosure that which is absent from the teachings of Katsube et al. that would lend guidance to the skilled artisan to extrapolate how to practice the instantly claimed invention without undue experimentation, given the apparent degree of unpredictability or seemingly inoperable embodiment of the claimed invention, especially given the state

of the art at the time the specification was originally filed and the state of the art post-date thereof. For example, like Kang, the results of the experiments using $Apc^{\Delta 716}$ knockout mice conducted by Oshima et al. (*Cell*, 1996; vol. 87, pp. 803-809. *"Suppression of Intestinal Polyposis in $Apc^{\Delta 716}$ Knockout Mice by Inhibition of Cyclooxygenase 2 (COX-2)"*.) indicate that induction of COX-2 is a very early event in the sequence of polyp formation to colon carcinogenesis and suggest that COX-2 plays a significant role in polyp development itself. Also like Kang, Oshima et al. teach that Apc^{MIN} mice can be used to test the potential of drugs to inhibit the growth and development of human colon cells. In another instance, Korobi et al. (*JARQ*, 2003; vol. 37, no. 3, pp. 159-165. *"In Vitro-Screening for Cancer-Suppressive Effect of Food Components*") teach, "Malvidin more selectively inhibited the growth of HL60 cells than that of HCT116 cells. Thus 50-200 μM malvidin reduced the number of viable HL60 cells to 3-25% of the control, whereas at 200 μM, this value was only 78% of the control for HCT116 (Fig. 8)", on page 164, second Column, first paragraph. Korobi et al. further teach that induction of apoptosis in HCT116 cells was minimal following treatment with 200 μM pure anthocyanidins, on page 164, last sentence in paragraph 2. Moreover, on page 165, Column 1, second paragraph, Korobi et al. teach that while delphinidin-glycosides isolated from bilberry extract inhibited the growth of HCT116 cells *in vitro*, malvidin-glycosides failed to inhibit the growth of HCT116 cells. Finally, Hou et al. (Biochemical Pharmacology, 2005; vol. 70, pp. 415-425. "*Anthocyanidins Inhibit Cyclooxgenase-2 Expression in LPS-evoked macrophages : Structure Activity Relationship and Molecular Mechanisms Involved*".) investigated the effects of

anthocyanidins on the expression of cyclooxgenase-2 (COX-2) in lipopolysaccharide (LPS)-activated murine macrophage RAW264 cells and demonstrated the molecular mechanism of inhibitory actions of anthocyanidins on COZX-2 expression. The data obtained in the Hou' study showed that the inhibitory effects of anthocyanidins on COX-2 expression depended on the *ortho*-dihydroxyphenyl structure on the B-ring, and delphinidin with this structure inhibited LPS-induced COX-expression by blocking the signaling cascades of MAPK with the attendant activations of NF-κB, C/EBPδ and AP-1. On page 419, second Column, under "*3. Results*" bridging page 420, Hou teaches, "According to the amount of the possible intake from fruits and vegetables or their concentrated commercial extracts, we treated RAW264 cells with typical five kinds of anthocyanidins (Fig. 1A) at 25-100 μM for 30 min before exposure to 40 ng/ml LPS for 12 h, and found that LPS-induced COX-2 protein was suppressed by addition of over 50 μM of delphinidin or cyanidin, but not suppressed by addition of over 100 μM of pelargonidin, peonidin or malvidin. Fig. 1B shows a representative result at 75 μM of delphinidin. LPS-induced COX-2 protein was significantly inhibited by75 μM of delphinidin or cyanidin, but not by pelargonidin, peonidin or malvidin ($P < 0.05$). The constitutive protein, COX-1, showed no change in such treatment. The *ortho*-dihydroxyphenyl structure on the B-ring of anthocyanidins appears to be essential for the inhibitory action because pelargonidin, peonidin and malvidin, having no such *ortho*-dihydroxyphenyl structure failed to show the inhibitory effect. The inhibitory actions by delphinidin and cyanidin were not caused by their cytotoxicity, because this concentration that suppressed COX-2 expression did not affect cell viability as

measured by MTT assay (data not shown). These results indicate that the delphinidin and cyanidin may be potential inhibitors for COX-2". Given the above cited, representative art teachings of the state of the art at the time the original application was filed and the state of the art post-date thereof, even in consideration of the Declaration under 37 C.F.R. § 1.132 filed on June 29, 2006 and its accompanying ATCC Product Descriptions of Exhibit A indicating that HCT-116 and AGS are art recognized *in vitro* models correlating to the specific conditions of human colon cancer and human stomach cancer, respectively; and even in consideration of the teachings of Gieseg et al. (*BMC Cancer*, July 2004; vol. 15, no. 4, pp. 35. "*The Influence of Tumor Size and Environment on Gene Expression in Commonly Used Human Tumor Cell Lines*", Appellants' arguments directed to the idea that the Examiner has not given reasons for the lack of enablement based on a lack or correlation for an *in vitro* or *in vitro* model are deemed moot. The foregoing also demonstrates that the lack of working examples in the specification supports a finding that the limited guidance by the disclosure does not enable the skilled artisan to practice it with undue experimentation. The specification fails to give the skilled artisan direction as to how to determine what a composition consisting essentially of malvidin actually consists of or how to extrapolate the dose amounts that would be effective in suppressing the multiplicity of human colon cells and human stomach cells in a mammal when the claim-designated composition is orally administered to a mammal in need of such treatment. Surely the state of the art at the time of filing of the present application and state of the art post-date state thereof suggests that Appellants' claimed invention does not work in recognized *in vitro* or *in*

vivo models mimicking the conditions of multiplicity of cancer cells in humans or mammals. Clearly, the teachings of Oshima, Korobi and Hou provide a sharp contrast to Appellants' disclosure that the viability of colon (HCT-116) and stomach (AGS) cells decreases in the presence of 100 ppm and 200 ppm of malvidin.

Predictability and State of the Art. Appellants did not specifically address the Examiner's analysis of the claimed invention in consideration of the particulars given in the previous Office action *per se* under the heading of "*Predictability and State of the Art*"; therefore the Examiner deems that the analysis of this factual consideration was proper.

Amount of Experimentation Necessary. With regard to the "*Amount of Experimentation Necessary*", Appellants argue that the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention. Thus, Appellants argue case law and cites the M.P.E.P., on page 14, line 13 to page 16 in its entirety of the Appeal Brief:

"A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In* re *Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of
experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In* re *Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

For example, as noted in M.P.E.P. §2164.01(c), it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd, sub nom., Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In* re *Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. Considering all of the above noted factual considerations, undue experimentation would not have been needed to make and use the claimed invention. Therefore, the claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells is enabled by the specification. Reversal of the rejection is requested."

In response to Appellants' argument that the determination of "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination but rather a conclusion reached by weighing all of the above noted factual considerations, the Examiner's complete analysis of the claimed invention with regard to all of the relevant *Wands* factors fully support a conclusion of lack of enablement for the claimed *in vivo* method for suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of cancer cells which comprises providing an effective amount of malvidin as an active ingredient to the mammal so as to suppress the multiplicity of the cells. Therefore, in

view of the breadth of the claims, the limited guidance of the specification as to how carry out the claimed invention, the lack of correlative working examples, and the state of the art at the time the specification was filed, the Examiner maintains that the claimed method for the *in vivo* suppression of multiplicity of either or both of any and all stomach and any and all colon cancer cells in a mammal comprising the administration of an effective amount of the claim-designated composition would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

Thus, it would take undue experimentation without a reasonable expectation of success for one skill in the art to provide the claimed method for *in vivo* suppression in a mammal of multiplicity in the stomach, colon and in both the stomach and colon of any and all stomach and/or any and all stomach cancer cells or the claim-designated AGS stomach cancer cell line or the claim-designated HCT 116 colon cancer cell line comprising providing the mammal with an effective amount of a composition consisting

essentially of malvidin to suppress multiplicity of the cancerous cells, as broadly claimed by Appellant.

Accordingly, a sufficient number of reasons have been given to arrive at a conclusion that the specification, while being enabling for an *in vitro* method for inhibiting the proliferation of colon cancer cells and stomach cancer cells comprising contacting the cells with an effective amount of a composition consisting essentially of malvidin, does not reasonably provide enablement for a method for *in vivo* inhibition in a mammal of proliferation in the stomach, colon and in both the stomach and colon of caner cells which comprises providing an effective amount of malvidin as an active ingredient to the mammal so as to inhibit the proliferation of the cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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